Response to Rejection under 35 U.S.C. § 112 ¶1

Claims 1-7 and 9-12 have been rejected under 35 U.S.C. § 112 ¶1 as non-enabled for the surfactants that are structurally different from polysorbate 20 and polysorbate 80. The Examiner further states that no criteria for "a stable G-CSF formulation" are set forth, the length of time the stability remains in effect is not cited, and that adequate information regarding the molar amounts of surfactants necessary to give rise to a stable G-CSF is not provided.

Applicants traverse the rejections under § 112 ¶1.

Applicants respectfully submit that the invention is properly enabled for surfactants other than polysorbate 20 and polysorbate 80. Nevertheless, applicants have amended Claims 1 and 7 to limit the scope of the claims of this application to non-ionic surfactants. This amendment should put all of the claims in condition of allowance, since the environment for stable conditions and structural similarity are made more similar by this limitation.

Applicants also respectfully submit that the criteria for stability and length of time said stability remains in effect are given in the specification. The Examiner may have overlooked the portion of the specification where the criteria for stability, including the length of time the stability remains in effect, are set forth. The Applicants, therefore, respectfully direct the Examiner to the portion of the specification where "stabilization" is defined (page 3, lines 9-12), as well as where stability of the formulations of the present invention is discussed (inter alia, page 15 line 11 through page 16 line 3). The definition on page 3 is reproduced below for the convenience of the Examiner:

> As used herein, stabilization means that the percentage of remaining G-CSF is kept at 95% or more after storage at 25°C for 6 months or 75% or more after storage at 40°C for 2 weeks.

Response to Rejection under 35 U.S.C. § 112 ¶2

Claims 1-12 have been rejected under 35 U.S.C. § 112 ¶2 as indefinite because use of the term "such as" in Claim 7 and the relative terms "at least," "less," and "substantially" in claims 1 and 6 allegedly render the claim limitations unclear.

The Applicants traverse these rejections under § 112 ¶ 2.

Claim 1 as amended does not have unclear limitations, since the term "less" has been removed, and the terms "at least" and "substantially" continue to have clear limitations in light of the specification. Therefore amended Claim 1 is believed to be in condition of allowance. Claim 7 has been amended to delete the phrase "such as," which the Applicants believe should put this claim in condition of allowance.

The term "less" has been removed from Claim 1, and the lower end of the pH range is indicated, as supported in the specification. The Applicants respectfully submit that use of the terms "at least" and "substantially" in original Claims 1 and 6 as well as in amended Claim 1 do not render the claim limitations unclear or indefinite.

The Examiner objected to the use of the term "at least" as it originally appeared in Claim 1. The term "at least" is commonly used claim language and is acceptable where the defined end of the range is supported in the specification and the open end of the range is not unreasonably limitless. Applicants respectfully submit that in the instant case, the defined end of the range, "at least one," is supported in the specification and the open end is limited by the proportionality claim language: "in an amount of 1 part by weight or less per part by weight of the granulocyte colony-stimulating factor." Moreover, in light of the amendment limiting the class of surfactants used in the formulation to non-ionic surfactants, a further limit is placed on the number of

surfactants that one skilled in the art would choose to select for use in this invention. Thus, use of the term "at least" in Claim 1 does not render the claim indefinite under § 112 ¶2.

The Examiner objected to the use of the term "substantially" as it originally appeared in Claim 6. In anticipation of a similar objection with respect to amended Claim 1, as this phrase now appears therein, the applicant addresses the objection herewith.

The term "substantially" is not uncommonly used claim language and is acceptable where one skilled in the art is able to draw the line between, for example, unavoidable impurities and essential ingredients. See, e.g., In re Marosi, 710 F.2d 799, 218 U.S.P.Q. 289 (Fed. Cir. 1983). In the instant case, the term "substantially" is used in the context "substantially free of protein as a stabilizer." It is the Applicants' belief that this phrase does not render amended Claim 1 indefinite; the invention is directed preferably to purified or recombinant G-CSF, which one skilled in the art would understand generally to be substantially free of protein. See specification p. 3, ll. 25-38, p. 4 ll. 7-13, p. 6 ll. 25-27. Moreover, the specification distinguishes the invention from formulations stabilized by addition of proteins. See specification p. 6, line 27 – p. 7, line 4. Thus, one skilled in the art would know or understand from the teaching of the specification the meaning of the term "substantially" as used in amended Claim 1, because the specification teaches with sufficient conciseness what is intended to be used to stabilize the G-CSF. Use of the term "substantially" in amended Claim 1, therefore, should not render the claim indefinite. If the Examiner would feel more comfortable with the term "essentially" in place of "substantially," the Applicants would be amenable to such language.

Duplicative Claims

The Examiner stated that claim 4 is duplicative of 5 and claim 12 is duplicative of claim 1.

The Examiner has stated that Claims 4 and 5 are duplicative of each other. The Applicants respectfully disagree. While Claim 5 and Claim 4 have overlapping subject matter, Claim 5 is narrower than Claim 4. Claim 4 recites a most preferred range of "0.4 to 0.8," and Claim 5 recites two especially preferred finite values ("0.4 or 0.8") in that range. See specification page 6, ll. 6-18. Thus, Claims 4 and 5 are not duplicative.

The Examiner also has stated that Claim 12 is duplicative of Claim 1 because it is directed to the same formulation. The Applicants respectfully disagree because Claim 12 recites the formulation in packaged product form not the formulation alone. If the Examiner feels that the claim should be directed to the package containing the formulation rather than the formulation within the package, the Applicants are willing to rewrite the claim in that form. For example:

> 12. A vial, ampoule or prefilled syringe comprising the granulocyte colony-stimulating factor-containing formulation of Claim 1.
>
> or
>
> 12. A product of manufacture comprising: a package containing the granulocyte colony-stimulating factor-containing formulation of Claim 1, said package selected from a vial, ampoule or pre-filled syringe.

Response to Rejection under 35 U.S.C. § 102(a or b)/103 (a) and 35 U.S.C. § 103(a)

Claims 1-12 have been rejected under either § 102(a) or (b) as anticipated by or alternatively obvious under § 103(a) over Michaelis et al. U.S. Patent No. 5,919,443 ('443) or U.S. 5,919,757 ('757). Claims 1-2 are further rejected under § 103(a) as obvious over '443, '757 and Woog, U.S. Patent No. 5,503,827 ('827).

Applicants traverse these rejections and respectfully submit that the claims are not anticipated by either Michaelis '443 or '757. These patents disclose use of surfactants in formulations, but are directed to different compounds and require different pH ranges than

Applicants' invention. Likewise, Applicants respectfully argue that the claimed invention is not obvious over '443 and '757, or '443, '757 and '827.

The '443 patent is directed to non-glycosylated G-CSF, as is the '757 patent. '443 Col. 2 lines 48-55; '757 Col. 2, lines 39-46. By contrast, the invention of the instant application is directed to glycosylated G-CSF (p. 1, lines 12-14; p. 9, lines 22-27). This separate scope of the claimed invention has been clarified in amended Claim 1, by adding the phrase "having a sugar chain." The glycosylated G-CSF has different physical properties and stability from non-glycosylated G-CSF. As described in the specification (p. 9, lines 22-27), the sugar chain of G-CSF has one or two terminal scialic acids, which may be cleaved during extended storage. Therefore, the lower range of pH claimed in the '443 and '757 patents cannot be used with the formulation of the present invention, which contains G-CSF having a sugar chain.

The Examiner states that the '443 patent teaches a stable G-CSF preparations containing surfactant in an amount no greater than that of G-CSF and with a pH about 7 or lower, citing claims 14 and Tables 5 and 9. The invention of '443, as set forth in the language of Claim 14, teaches that it is the sugar that is the stabilizing agent, not the surfactant. Col. 20, lines 22-24, and Claims 15, 16 and 28; see also Col. 3 lines 9-12 and Claims 1, 2, 3 and 13. By contrast, the present invention uses surfactants as stabilizing agents. See, e.g., p. 2, line 25 – p. 3, line 1. While the '443 specification suggests that "low amounts of surfactant... are adequate to stabilize G-CSF," the patent does not teach that low amounts of surfactant are stabilizing at pH's between 5-7, as claimed in the present invention.

Every example in the '443 patent that teaches a formulation containing an amount of surfactant within the low range claimed in the present invention also teaches stability only at pH outside the range claimed in the present invention, i.e., below 5 or above 7. Example 6 teaches

0.2 part by weight and 0.33 parts by weight of surfactant to part G-CSF for formulations 15 and 16, but at pH 4.5 only; Table 9 teaches 0.28 parts by weight of surfactant to part G-CSF for formulations 17-24, but only at pH 4.5 or 7.2, both outside the range claimed in the present invention.

By the same token, where stability is indicated within the pH range of the present invention, the examples of the '443 patent teach use of surfactant in amounts well above those claimed in the present invention. Table 5 presents data for the formulations found in Table 4; the formulations having a pH within the range claimed in the present invention (i.e., formulations 8 and 10, pH 6.5) contain 20 parts by weight of surfactant to parts G-CSF, well outside the amounts claimed in the present invention. Likewise, Table 6 teaches 20 parts by weight of surfactant per part G-CSF at pH 7 for formulations 11-14.

Examiner also identifies Table 2 as an example anticipating the present invention, but formulation 5 contains an amount of surfactant (1.43 parts by weight per part G-CSF) outside the range claimed in the present invention at a pH (3.6) outside the range claimed in the present invention.

The '757 patent does not anticipate the present invention because it is directed to formulations with a desired pH range of 4-5 or 7-8. Col. 3, lines 26-31; Col. 4, lines 27-28, 54-56, 60-62; Col. 5, lines 1-3, 5-7, 10-12, 15-17, 39-41. The specification specifically states that the buffers of the '757 invention are unsuitable in the pH 5-7 range. Col. 9, lines 41-45. Stability data for solutions at pH 7 were conducted for cold storage, not storage at ambient or warm temperatures, where degradation is more likely. Table 5b, for which storage temperature is not indicated, relates to the formulations of Table 5a, in which the formulation having pH 6.5 also contains albumin, a stabilizing protein explicitly excluded from the scope of the present

invention. For the above-stated reasons, the '757 does not anticipate, but rather teaches away from the present invention.

The '443 and '757 patents do not render the present invention obvious, because neither patent teaches or suggests that stability can be achieved using surfactants as stabilizers in formulations within the pH 5-7 range, as claimed in the present invention. One skilled in the art would not be motivated to utilize the formulations of '443 or '757 at pH 5-7 with surfactants in an amount of 1 part by weight or less per part of G-CSF with any reasonable expectation of success, because such a skilled artisan would read the '443 and '757 patents to exclude this pH range as stable unless much larger amounts of surfactant are used or unless proteins are added as stabilizers. Moreover, as indicated above, these patents in fact teach away from the formulations of the present invention.

The Woog patent ('827) in combination with the '443 and '757 patents also does not render the present invention obvious. Being drawn to a formulation of G-CSF containing a surfactant and having pH of about 4.5, the '827 invention provides no motivation to one of ordinary skill in the art to use low levels of surfactants as stabilizers in a G-CSF formulation of pH 5-7 to achieve a stable liquid formulation. The '827 is directed to use of preservatives in formulations, and the specification teaches that sugars, not surfactants, may be used as stabilizers; stabilization is not at issue in the '827 patent. Examples 4-7 of '827 teach formulations of G-CSF containing surfactant; example 7 also contains urea, and therefore is not relevant to the present invention, and examples 3, 4 and 5 have pH's of 2.5, 4.5 and 3.8-4.0 respectively, all outside the range claimed in the present invention. Therefore, the '827 patent discloses nothing additional in view of the '443 or '757 patents that would render obvious the present invention as now claimed.

CONCLUSION

For the above-cited reasons, the Applicants believe that claims 2-5 and 10-12 and amended claims 1 and 7 are patentable, and a timely Notice of Allowance is respectfully requested.

AUTHORIZATIONS

The Commissioner is hereby authorized to charge any additional fees which may be required for timely consideration of this Amendment under 37 C.F.R. §§1.16 and 1.17, or credit any overpayment to Deposit Account No. 13-4500 Order No. 0263-4047.

Respectfully submitted,
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APPENDIX I

Below are the pending claims as amended. Deleted items are bracketed, added items are underlined.

1. (Amended) A stable granulocyte colony-stimulating factor-containing formulation comprising a granulocyte colony-stimulating factor having a sugar chain and at least one pharmaceutically acceptable non-ionic surfactant in an amount of 1 part by weight or less per part by weight of the granulocyte colony-stimulating factor and having a pH of 5-7 [or less], said formulation being substantially free from protein as a stabilizer.

2. The granulocyte colony-stimulating factor-containing formulation of Claim 1 wherein the surfactant is contained in an amount ranging from 0.2 to 1 parts by weight per part by weight of the granulocyte colony-stimulating factor.

3. The granulocyte colony-stimulating factor-containing formulation of Claim 1 wherein the surfactant is contained in an amount ranging from 0.2 to 1 parts by weight per part by weight of the granulocyte colony-stimulating factor.

4. The granulocyte colony-stimulating factor-containing formulation of Claim 2 wherein the surfactant is contained in an amount ranging from 0.4 to 0.8 parts by weight per part by weight of the granulocyte colony-stimulating factor.

5. The granulocyte colony-stimulating factor-containing formulation of Claim 2 wherein the surfactant is contained in an amount of 0.4 or 0.8 parts by weight per part by weight of the granulocyte colony-stimulating factor.

6. (Deleted) [The granulocyte colony-stimulating factor-containing formulation of Claim 1, which is substantially free from protein as a stabilizer.]

7. (Amended) The granulocyte colony-stimulating factor-containing formulation of Claim 1 wherein the surfactant is at least one [member] non-ionic surfactant selected from the group consisting of [nonionic surfactants such as] sorbitan fatty acid esters, glycerin fatty acid esters, polyglycerin fatty acid esters, polyoxyethylene sorbitan fatty acid esters, polyoxyethylene sorbitol fatty acid esters, polyoxyethylene glycerin fatty acid esters, polyethylene glycol fatty acid esters, polyoxyethylene alkyl ethers, polyoxyethylene polyoxypropylene alkyl ethers, polyoxyethylene alkyl phenyl ethers, polyoxyethylene hardened castor oils, polyoxyethylene beeswax derivatives, polyoxyethylene lanolin derivatives, and polyoxyethylene fatty acid amides[; cationic surfactants such as alkyl sulfates, polyoxyethylene alkyl ether sulfates, alkyl sulfosuccinic acid ester salts; and natural surfactants such as lecithin, grycerophospholipids, sphingophospholipids, sucrose fatty acid esters].

8. The granulocyte colony-stimulating factor-containing formulation of Claim 1 wherein the surfactant is a polyoxyethylene sorbitan fatty acid ester selected from the group consisting of Polysorbate 20 and Polysorbate 80.

9. (Deleted) [The granulocyte colony-stimulating factor-containing formulation of Claim 1, which has a pH of 5-7.]

10. The granulocyte colony-stimulating factor-containing formulation of Claim 1, which has a pH of 6-6.8.

11. The granulocyte colony-stimulating factor-containing formulation of Claim 1, which has a pH of 6.2-6.8.

12. The granulocyte colony-stimulating factor-containing formulation of Claim 1, which is packed in a vial, ampoule or prefilled syringe.